

Appl. No. : 09/923,870  
Filed : August 6, 2001

#### REMARKS

Claims 1-48 have been cancelled and new Claims 49-65 have been amended. Thus, Claims 49-65 are presented for examination. No new matter has been added by this amendment. Applicant wishes to thank the Examiner for her examination of the pending claims.

Support for the new claims can be found in the specification from pages 6-8, which corresponds to the description of Figures 1 and 2.

#### Oath/Declaration

The Examiner argued that the application, as filed, presented claims for subject matter that was not originally embraced by the statement of the invention. Applicant respectfully traverses, and argues that the claims corresponded with those of the original parent application. However, solely to advance prosecution of this application, Applicant will file an updated oath by the inventor in a supplemental filing. For this reason, Applicant respectfully requests withdrawal of the rejection.

Applicant has also amended the specification to indicate that this application is a continuation-in-part of U.S. Application Number 09/243,022, as requested by the Examiner.

#### Discussion of Rejection Under 35 U.S.C. § 101

The Examiner rejected Claims 41-48 as allegedly being directed towards non-statutory subject matter. Applicant respectfully disagrees. However, as these claims have been cancelled, this rejection is now moot.

#### Discussion of Rejection Under 35 U.S.C. § 112

The Examiner rejected Claims 24-48 for allegedly introducing new matter. Applicant respectfully disagrees. However, as these claims have been cancelled, this rejection is now moot.

#### Discussion of New Claims

Applicant respectfully disagrees with the Examiner regarding the patentability of cancelled Claims 24-48. However, in order to advance prosecution, Applicant has introduced

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new Claims 49-64 in an attempt to address many of the issues raised by the Examiner.

For example, the Examiner argued that the specification did not describe ways of carrying out the claimed methods that were not within a computer. Applicant notes that the new Claims 49-65 relate to methods performed in a computer.

The Examiner also commented that a metabolic network is more than a table of reactants and products. Applicant notes that Claims 49-65 relate to stoichiometric matrices including substrates, products and stoichiometry of the metabolic genes in the organism. Moreover, the claimed *in silico* representation of a microbe includes calculating uptake rates of metabolites and metabolic demands on the microbe. Those uptake rates and metabolic demands are combined with the stoichiometric matrix to produce an *in silico* representation of the microbe by performing a flux balance analysis on the combined stoichiometric matrix.

#### Enablement

##### *Assignment of Metabolic Genes*

The Examiner alleged that the specification does not enable one of ordinary skill in the art to know if a nucleic acid sequence corresponds to a metabolic gene, nor how to determine what its reactants, products or stoichiometry would be. Applicant strongly disagrees.

Several factors need to be considered to properly determine whether the specification enables one of ordinary skill in the art to practice the claimed invention without undue experimentation (*In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)). These factors include: 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented in the application; 3) the presence or absence of working examples of the invention in the application; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability in the art; and 8) the breadth of the claimed invention.

It should be noted that a considerable amount of experimentation is permissible, if it is merely routine (*Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982). In addition, experimentation can be 'tedious and laborious,' and nevertheless 'routine' (*Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982). Experimentation requiring only routine optimization or

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screening has not been held to be undue experimentation because "[e]nablement is not precluded by the necessity for some experimentation such as routine screening" (*In re Wands*).

Beginning on page 7, last paragraph, the specification first defines metabolic genes as the subset of genes involved in metabolic reactions and functions in a cell. The gene products produced from this subset carry out all or most of the enzymatic reactions and transport reactions known to occur within the target organism. The specification teaches that in order to select metabolic genes, one can search for genes involved in central metabolism, fatty acid and lipid metabolism, carbohydrate assimilation, vitamin and cofactor biosynthesis and energy and redox generation. Accordingly, the specification particularly defines genes that are within the class of "metabolic genes" so that one of ordinary skill in the art would know whether a nucleic acid sequence corresponded to a metabolic gene.

Moreover, as stated throughout the specification, many metabolic pathways of microbes are known, as are many of the genes that encode the enzymes used in those metabolic pathways. Thus, by looking at the function of a protein encoded by a particular gene, one can determine from that function whether or not it is a metabolic function. In addition, the application provides a working example of determining which genes from *E. coli* K-12 are metabolic genes. Thus, one of ordinary skill in the art could use the teachings of the specification, along with the working example, to determine if a gene from another microbe was a metabolic gene. For all of these reasons, Applicant respectfully requests withdrawal of this rejection.

#### *Assignment of Genes to a Metabolic Network*

The Examiner argued that, for a large number of organisms, the metabolic reactions and pathways are not known. In addition, in many cases, knowledge of an enzyme present in an organism does not provide any information on how the enzyme fits within a metabolic network. For this reason, the Examiner argued that one of ordinary skill in the art would not be enabled to practice the claimed invention. Applicant respectfully disagrees.

Initially Applicant notes that the pending claims relate to methods of producing stoichiometric matrices, or *in silico* representations, of microbes. The metabolic pathways of many microbes were well-known at the time the application was filed, and more information is being developed each day. Moreover, when analyzing the metabolism of a single cell, such as a

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microbe, it is not necessary to understand how the enzyme fits within the metabolic network. Knowledge of the actual metabolic pathways is not required to create a stoichiometric matrix. For each enzyme, only the reactants, products and stoichiometry of each reaction need to be known. Thus, in a vast majority of cases, determining the enzymatic function of a particular enzyme would lead to an accurate assignment of that microbial gene, and its related reactants, products and stoichiometry to a genome specific stoichiometric matrix. For this reason, once the function of a gene product in the microbe is identified, it can be accurately placed within the stoichiometric matrix, even if no information is known for the enzymes place in a metabolic network. For this reason, Applicant respectfully requests withdrawal of this rejection.

#### *Functional Assignment of Genes*

The Examiner continues to maintain that the specification does not provide enough guidance on how to assign a function to the gene product of an unknown metabolic gene, when all this is know is its homology to other known genes. The Examiner alleged that, for example, assigning the function of "kinase" based upon homology did not provide the substrate and product of that reaction. Applicant strongly disagrees.

The claims relate to methods of generating genome specific stoichiometric matrices and *in silico* representations of microbes by, in part, assigning a function to a metabolic gene based on its nucleotide or amino acid homology to other, known metabolic genes. While the Examiner maintains that the specification does not include enough information on how to perform such homology based determinations, Applicant argues that this type of experiment was well within the skill of the ordinary artisan at the time the application was filed.

As taught in the specification, a homology search can be run to determine how similar the metabolic gene is to the known gene (page 7, second full paragraph). The Examiner inquired as to what degree of homology would lead one of ordinary skill in the art to the conclusion that a nucleic acid corresponded to a metabolic gene. Of course, one of ordinary skill would realize that if the similarity was 100%, the metabolic gene would be the same as the known gene and assign the function accordingly.

One of ordinary skill in the art could also follow the teachings of the specification, along with what is well-known in the art regarding homology matching of sequences, to determine

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whether or not to assign a particular function to an unknown nucleotide sequence when the homology was less than 100%. For example, one of ordinary skill in the art would immediately recognize that unknown genes that are almost 100% identical to a known gene, but from a different microbe, would be very likely to encode a gene product having the same reactants, products and stoichiometry as the known gene. While this may not be true for every case, enablement does not require one-hundred percent certainty. It only requires that the level of experimentation be "routine" and not "undue." See In re Wands.

One of ordinary skill in the art would understand the evolutionary differences between microbes, and know that some microbes would be expected to have gene products with high homology to the unknown gene, and some organisms would not. Moreover, one would understand that some families of genes are highly conserved, and thus would be expected to vary little from one species to another. In contrast, some families of genes are not well conserved, and thus would be expected to have greater genetic difference between families. This is all well known to the skilled artisan in molecular biology.

This type of analysis and balancing of factors was well within the purview of one of ordinary skill in the art at the time the application was filed, and requires no more than the concept of using homology matching to discern whether or not an unknown metabolic gene may have the same reactants, products and stoichiometry as a similar gene from a different organism. This concept is discussed at length in the specification. On a daily basis, researchers compare the homology of one gene, or gene product, to another and decide their relatedness and chance for being involved in the same reaction.

Applicant argues that only "merely routine" testing would be required of a skilled artisan armed with Applicants' roadmap for performing homology searches against databases of genes with assigned functions. As stated in *Wands* "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In this case, the specification provides sufficient guidance so that one of ordinary skill in the art could make a functional assignment of an unknown gene.

Moreover, even if the initial functional assignment was incorrect, one of ordinary skill in the art could perform additional homology matches to determine the correct functional assignment

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so that an accurate genome specific stoichiometric matrix was produced. For all of these reasons, Applicants respectfully request withdrawal of the enablement rejection.

#### CONCLUSION

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding notice. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above.

Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

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